HERMES: Messenger for Stroke Interventional Treatment

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The treatment approach for acute ischaemic stroke is straightforward: restore blood flow; do it as soon as possible; and as safely and completely as possible. The over-long path to confirming this simple and intuitive treatment plan leads to today's publication of the HERMES collaborators' individual patient data meta-analysis, combining the five clinical trials of endovascular mechanical thrombectomy (MT) published in 2015.[1-5] The total of 1287 patients across these studies allows more precise estimates of overall treatment effect, and strengthens conclusions regarding the consistency of effects across major subgroups of age and severity. The number needed to treat to reduce disability by at least 1 level on the modified Rankin Scale (mRS) of 2.6 is extraordinary in itself and represents a huge advance in care for those patients with stroke caused by occlusion of the major intracranial carotid-territory vessels, whose response to optimal medical care with IV thrombolytic drugs is limited,[6] leaving a high proportion dead or disabled. Updates to European and North American guidelines for acute stroke management have already reflected the published individual trials in recommending MT in suitable patients, conclusions that are supported by the HERMES analysis.[7-9]

The meta-analysis justifiably omits earlier trials (most notably the IMS-3 trial)[10] since these were conducted in an era where radiographic confirmation of arterial occlusion by CT angiography was not widely available, and intervention used first-generation thrombectomy devices that were subsequently established as less effective and potentially more hazardous than the stent-retriever devices that constitute the vast bulk of the evidence included in HERMES.[11,12] The reported revascularisation rate of 70.5% is a standard achievable in expert units using the current generation of MT devices. Experience shows that clinical success cannot be assumed because of revascularisation rates and new technology alone, however,[13] and replicating the highly efficient networks of care that delivered these trials, exemplified by the very short median symptom onset-to-treatment times for IV thrombolysis of 100 minutes, represents a major challenge for many healthcare systems.

The individual patient data meta-analysis approach glosses over differences among the component trials that were arguably more evident in group-level meta-analyses.[14] Outcomes in the control arms across the five individual trials included in HERMES were markedly different (eg mortality ranged from 12% to 22% and excellent functional recovery defined by mRS scores of 0-1 ranged from 6% to 28%), suggesting that either the application of stated inclusion and exclusion criteria resulted by chance in very different patient selection across trials, or, more likely, that additional, non-protocol factors in patient selection were at work. The potential for additional, uncharacterised, selection biases reflects the circumstances of the trials. The HERMES trials were undertaken predominantly by small numbers of highly expert, high-throughput neuroscience-based stroke centres and in a very select group of patients, (limited screening data[2] indicate that perhaps only 1% of stroke patients were included, and around 7% of those eligible for IV rtPA). Around one third of patients were transferred to trial neurovascular centres from primary stroke centres (after initiation of IV rtPA), and criteria determining patient transfer decisions are not characterised.

Additional imaging selection using perfusion imaging or collateral imaging in three of the five HERMES trials [2-4] is a strategy that maximises trial efficiency by focusing on patient groups with the greatest likelihood of benefit, but inevitably leads to a larger absolute treatment effect (and thus lower number needed to treat) estimate than if treatment were applied to less rigorously selected patients. The potential for imaging selection to select out those at very high risk of poor outcome is suggested by two of these three trials individually reporting MT to reduce mortality by 9-11%,[2,3] an effect not evident in the pooled analysis. The role for additional perfusion or collateral vessel imaging, and comparison of these different approaches, requires further research, as does the interaction with extensive early ischaemic features on routine CT brain imaging (only 121 patients had an ASPECT score 0-5, signifying more extensive early ischaemic change). Absolute treatment

effects will ultimately determine the cost-effectiveness of the intervention, and robust cost-effectiveness modelling is required, including the potentially large set-up costs for countries that lack the infrastructure for MT delivery. Establishing broad applicability and characterising the absolute treatment effects in wider populations will require systematic collection of registry data.

Subgroup definitions are constrained by the original trial selection criteria and framed to ensure reasonable sample size, but several clinically important areas are under-represented. While older patients were better represented than in previous acute stroke trials, only 15% were 80 years of age or over. The same proportion had contraindications to IV thrombolysis, but this is a broad and undefined group. The trials covered only a very narrow range of time windows, regardless of protocols (only 208 patients were randomised later than 5 hours from onset, and only 69 patients beyond 6 hours) Lack of statistical heterogeneity is not the same as evidence of efficacy when many major subgroups are so small, and implementation of MT in circumstances such as late presentation, extensive early ischaemic change on CT, or ineligibility for IV rtPA should be cautious, or wherever possible, await further trial evidence. Use of MT in more distal anterior circulation vessels (middle cerebral artery M2 and beyond) and in the posterior circulation remain unproven. Technical issues including whether general anaesthesia or sedation should be used as primary approach, the place for aspiration techniques, need for balloon guiding catheter, adjunctive stenting of co-existing carotid stenosis, additional intra-arterial thrombolytic drugs and so forth, remain unanswered.

Two further trials of MT (THRACE and THERAPY) have presented their preliminary results and remain unpublished, while a third (PISTE) is due to present results shortly.[15] All of these were terminated prematurely after interim review triggered by the results from the HERMES trials. These unpublished trials include a further 587 patients, predominantly treated within similar timelines and primarily with stent-retrievers. Whether results will modify HERMES' conclusions regarding effect size, and extend knowledge of subgroups, remains to be seen. Nonetheless, the efficacy of endovascular MT in anterior circulation stroke due to large artery occlusion is established, and implementation for those patients represented in the trials should be the priority. Further trials remain vital to clarify the boundaries of treatment.

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